DATA EVALUATION RECORD

DICAMBA

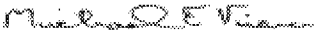
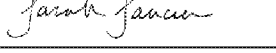
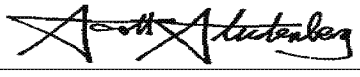
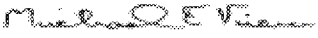
Study Type: OCSPP Non-Guideline; [^{14}C]-Dicamba: Duodenum Kinetics in Rats

EPA Contract No. EP-W-16-018
Task Assignment No. 34-3-001 (MRID 51129104)

Prepared for
Health Effects Division
Office of Pesticides Program
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

Prepared by

10560 Arrowhead Dr., Suite 500
Fairfax, VA 22030

Primary Reviewer:	Signature:	
Michael E. Viana, Ph.D.	Date:	08/14/2020
Secondary Reviewer:	Signature:	
Sarah E. Saucier, Ph.D.	Date:	08/25/2020
Quality Assurance:	Signature:	
Scott D. Studenberg, Ph.D., DABT	Date:	08/27/2020
Project Manager:	Signature:	
Michael E. Viana, Ph.D.	Date:	08/31/2020

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by CDM/CSS-Dynamac Joint Venture personnel. Contractor's role did not include establishing Agency policy.

EPA Reviewer: Sarah Dobreniecki **Signature:** Sarah Dobreniecki
Risk Assessment Branch VII, HED (7509P) **Date:** 9/16/2020
Template version 02/06

DATA EVALUATION RECORD

STUDY TYPE: Mechanistic Follow-Up Study in Rats; OCSPP Non-Guideline; OECD 489.

PC CODE: 029801

DP BARCODE: D458715

TXR #: 0058082

TEST MATERIAL (RADIOCHEMICAL PURITY): [^{14}C]-Dicamba (99% a.i.)

SYNONYMS: BAS 183 H; SAN837 technical; 3,6-dichloro-2-methoxybenzoic acid

CITATION: Hilton, A. (2020) [^{14}C]-Dicamba: duodenum kinetics in rats. Covance CRS Ltd., Alconbury, Huntingdon, Cambridgeshire, UK. Laboratory Study No.: MT42NJ, February 28, 2020. MRID 51129104. Unpublished.

SPONSORS: Syngenta, Ltd., Jealott's Hill International Research Centre, Bracknell, Berkshire, UK

BASF SE, Carl-Bosch-Strasse 38, Ludwigshafen am Rhein, Germany

EXECUTIVE SUMMARY: In a concurrently-reviewed, non-guideline, *in vivo* comet test (MRID 51129101), increased DNA strand breaks accompanied by increased numbers of hedgehog cells were observed in the duodenum of Crl:CD(SD) male rats administered dicamba in aqueous 0.5% methylcellulose via oral gavage (dose volume 10 mL/kg) at dose levels of 37.5 or 75 mg/kg/day. The present study was performed to obtain the absorption kinetics and rates and routes of excretion of dicamba following oral administration to rats. In this non-guideline, absorption kinetics follow-up study (MRID 51129104), groups of four Crl:CD(SD) male rats were administered [^{14}C]-dicamba (radiochemical purity 99%, batch # WJE-I-57) in aqueous 0.5% methylcellulose via oral gavage (dose volume 10 mL/kg) at a dose level of 75 mg/kg/day; two doses were administered approximately 24 hours apart. At approximately 0.5, 1, 2, 4, or 6 hours after the second dose, the rats were euthanized. Whole blood and plasma, duodenum sections, mincing solutions and scrapings, liver sections, and urine samples were obtained at each time point and analyzed for radioactivity.

No clinical signs of toxicity were reported.

[^{14}C]-Dicamba is rapidly absorbed after oral gavage administration. The maximum concentration of [^{14}C]-dicamba in whole blood was observed at 0.5 hours after the second dose and declined steadily to the final 6-hour sample. Similarly, the maximum concentration of [^{14}C]-dicamba in plasma was observed at 0.5 hours after the second dose and declined steadily to

the final 6-hour sample. Plasma concentrations were consistently greater than those in whole blood.

In the duodenum sections, mean total radioactivity and mean concentration of radioactivity were greatest at 0.5 hours after the second dose and declined with time. Concentrations were still measurable at 6 hours after the second dose. Concentrations in duodenum sections were greatest in section A (immediately after the stomach) and declined from sections A to B and generally declined from sections B to C between 0.5-2 hours after the second dose. At 4 and 6 hours, mean concentrations were generally similar across all sections. Mean total radioactivity and mean concentrations of radioactivity in the mincing solutions and scrapings were less than those found in the duodenum sections and followed the same time course, approaching the limit of quantitation at 6 hours. Mean concentrations of radioactivity in the liver sections were greatest at 0.5 hours after the second dose and declined with time to 6 hours.

Radioactivity was detectable in the urine at 1 hour following the first dose with the greatest concentration at 4 hours. Radioactivity concentrations fell to the lowest concentration at 24 hours after the first dose. Following the second dose, radioactivity began to rise, with the greatest concentration at 2 hours after the second dose and falling with time to the final collection at 6 hours.

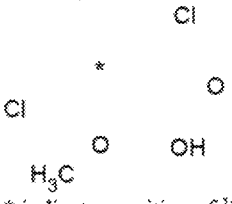
This study is classified as **acceptable / non-guideline**.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, Flagging, and Quality Assurance statements were provided.

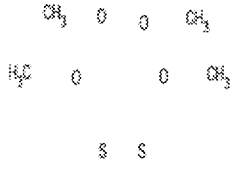
I. MATERIALS AND METHODS

A. MATERIALS

1. Test compounds:

Radiolabeled test compound:	[Phenyl-U-^{14}C]-SAN837H (dicamba)
Radiochemical purity:	99% (TLC)
Specific activity:	182.5 µCi/mg (6.75 MBq/mg)
Batch #:	WJE-I-57
Expiration/storage:	February 29, 2020 / ≤ −80°C
Structure:	

* indicates position of ^{14}C-label

Non-Radiolabeled TGAI:	Dicamba
Description:	White solid
Lot #:	P.MG2726410
Purity:	89.8% a.i.
CAS # of TGAI:	1918-00-9
Expiration/storage:	Approximately ten years stored at <30°C
Structure:	

2. Vehicle: Aqueous 0.5% (w/v) methylcellulose (batch # and source not provided).

3. Test animals

Species:	Rat (male only)
Strain:	Sprague Dawley [Crl:CD(SD)]
Age / weight at Day 1:	Approximately 1-2 months / 220-256 g
Source:	Charles River UK Ltd. (Margate, Kent, England)
Housing:	During acclimation, rats were housed up to 5/cage in solid-bottom polycarbonate cages with stainless steel lids and wood-flake bedding. Environmental enrichment (wooden chew block and plastic shelter) were provided. After dosing, rats designated for excretion phases were housed individually in glass metabolism cages; rats in the other sub-groups were returned to their battery cages.
Diet:	VRF1 diet, *ad libitum*.
Water:	Tap water, *ad libitum*.
Environmental conditions	
Temperature:	20-24°C
Humidity:	40-70%
Air changes:	Not provided
Photoperiod:	12 hours light/12 hours dark
Acclimation period:	4-5 days minimum

4. Preparation of dosing solutions: It was stated that method suitability and formulation homogeneity were established by using a trial dose prior to dose formulation (no further

details provided). A stock solution of [^{14}C]-dicamba was prepared by dissolving the radiolabel in acetonitrile (0.5 mL) and mixing by inversion until dissolved. The stock solution was stored at −70°C ± 10°C. The dose formulations were prepared by first combining [^{14}C]-dicamba and non-labeled dicamba in acetonitrile to yield the desired specific activity. This dilution was placed in a mortar and dried under a stream of nitrogen. The vehicle (aqueous 0.5% [w/v] methylcellulose) was added and the radiolabel suspended with a mortar. This suspension was transferred to a dose vessel (not described), stirred continuously, and sonicated. Formulation details are presented in Table 1.

TABLE 1. Dose preparations. [a]

Parameter	Day 1	Day 2
Weight [^{14}C]-dicamba (mg)	5.018	4.908
Weight non-labeled dicamba (mg)	524.76	531.941
Volume of vehicle (mL)	70	70
Calculated specific activity (dpm/mg)	3867430	3791451
Concentration of [^{14}C]-dicamba (mg/mL)	7.497	7.599
Volume administered (mL/kg)	10	10

a Data obtained from Appendix 2 on pages 44-45 of MRID 51129104.

Triplicate portions of each formulation were sampled pre- and post-dosing and assayed by liquid scintillation counting (LSC).

B. STUDY DESIGN AND METHODS

1. In-life dates: Not reported.

2. Animal assignment: Study details are presented in Table 2. Following receipt, the rats were weighed and randomly assigned to the groups. No additional information was reported.

TABLE 2. Absorption kinetics and excretion study after administration of [^{14}C]-dicamba by two oral gavage doses of 75 mg/kg/day to rats. [a]

Group	Number of Rats	Sampling time (hours)	Body weight (g) [b]		Dose administered (mg) [b]		Dose administered (mg/kg/day) [b]	
			Day 1	Day 2	Day 1	Day 2	Day 1	Day 2
1	4	0.5	228 ± 6	235 ± 8	17.05 ± 0.48	17.95 ± 0.65	74.9 ± 0.4	76.3 ± 0.3
2	4	1	238 ± 10	247 ± 7	17.80 ± 0.89	18.71 ± 0.36	74.8 ± 0.6	75.9 ± 0.7
3	4	2	241 ± 9	247 ± 9	17.99 ± 0.53	18.71 ± 0.57	74.7 ± 0.6	75.9 ± 0.7
4	4	4	248 ± 5	256 ± 5	18.55 ± 0.37	19.57 ± 0.38	74.8 ± 0.4	76.5 ± 0.7
5	4	6	240 ± 11	248 ± 11	17.99 ± 1.02	18.81 ± 0.66	75.1 ± 0.8	75.9 ± 0.9

a Data were obtained from page 17 and Appendix 2 on pages 44-45 of MRID 51129104.
b Mean ± SD calculated by the Reviewers.

3. Dosing and sample collection

a. Dose selection: The 75 mg/kg/day dose level was used in previously performed comet test (MRID 51129401).

b. Dosing: The dose suspensions were administered by oral gavage at a dose volume of 10 mL/kg; the volumes were calculated from the Day 1 and 2 body weights. The dose

suspensions were administered twice approximately 24 hours apart. The mean (± SD) doses administered for each group are shown in Table 1.

All rats were observed immediately after dosing, at approximately 1-2 hours post-dosing, and at least one other time during the day for clinical signs of toxicity.

c. **Sample collection:** At the times specified in Table 2, the rats were anesthetized with isoflurane and blood samples (approximately 8 mL) were obtained by cardiac puncture. Duplicate portions (50 µL) were removed for radioanalysis and the remaining portion was centrifuged to yield plasma. Duplicate portions (50 µL) of plasma were removed for radioanalysis. The rats were euthanized by cervical dislocation and the duodenum, remaining gastrointestinal tract (including contents), and liver were excised; the residual carcass was retained but not analyzed. The duodenum was isolated and three 2-cm lengths were cut starting from the stomach. The sections were rinsed with mincing solution (not described) and scraped clean; each section was then placed in a separate scintillation vial.

Urine and feces were collected separately from the rats of Group 5 (6-hour sampling time) only. Urine was collected from each rat at 0-1, 1-2, 2-4, 4-6, and 6-24 hours after the first dose and 0-1, 1-2, 2-4, and 4-6 hours after the second dose. Feces were collected during 0-24 hours after the first dose and 0-6 hours after the second dose; the cages were washed with water (100 mL) at each feces collection. The urine and feces containers were cooled with dry ice.

All samples were stored at −20°C ± 10°C until analysis.

4. **Sample treatment:** Treatment of the fecal samples was not discussed and fecal results were not reported.

a. **Urine:** The urine samples were thawed and weighed, and duplicate weighed portions were added directly to scintillation solvent.

b. **Duodenum:** The duodenum sections were weighed and digested with a tissue solubilizer (Goldisol) at approximately 55°C until the digestion was complete. The digest was mixed with scintillation solvent.

c. **Mincing solution:** The mincing solution from each duodenum section was weighed and solubilized in a mixture of water, methanol, and Triton X-405 (6:3:1; v/v) with 80 g/L sodium hydroxide at approximately 55°C until the digestion was complete. The digest was weighed, and duplicate weighed portions were added directly to scintillation solvent.

d. **Liver:** The liver samples were thawed, weighed, and mechanically homogenized. Duplicate weighed portions were digested with tissue solubilizer as for duodenum sections. The digest was mixed with scintillation solvent.

e. **Blood and plasma:** Duplicate weighed portions of blood and plasma were removed for radioanalysis; plasma was added directly to scintillation solvent and blood was combusted.

5. **Analytical methodology**

a. **Combustion analyses:** Blood samples were combusted with a sample oxidizer. Combustion products were trapped with a commercially-available absorbent and mixed with scintillation solvent. Recovery tests were conducted by combusting a commercial standard fortified with appropriate radioactivity, and efficiency was generally >95%. Radioactivity measurements were corrected for combustion efficiency.

b. **Liquid scintillation counting (LSC):** Radioactivity was measured using LSC having automatic quench correction (additional details not provided). Background levels were determined and radioactivity less than twice background was considered below the limit of quantification.

c. **Thin-layer chromatography (TLC):** Radiochemical purities of the stock solution and dose formulations were determined by TLC. TLC was conducted with commercially-available normal phase plates (silica gel 60 F_{254}, 0.25 mm thickness) with a toluene:acetone:acetic acid (65:35:5, v:v) solvent system. Linear-scaled radiochromatograms were visualized with an image analyzer (FLA-5000; Fuji Photo Film Co., Japan) and software.

6. **Statistics:** Statistical analyses were not conducted. Mean ± standard deviation (SD) or individual data were reported. Data below the limit of quantification were reported as BLQ.

II. RESULTS

A. RADIOLABELED DOSE

1. **Radiochemical purity:** The radiochemical purities of the stock solution and Day 1 and 2 dose formulations as determined by TLC were 99.7%, 99.9%, and 99.7%, respectively.

2. **Dose levels:** The mean actual doses administered are presented in Table 2. The actual doses administered ranged between 99.6-102.0% of the nominal dose levels.

B. CLINICAL SIGNS: No treatment-related clinical signs of toxicity were observed.

C. ABSORPTION/PHARMACOKINETICS

1. **Whole blood and plasma kinetics:** Whole blood and plasma kinetics are presented in Table 3. The maximum concentration of [^{14}C]-dicamba in whole blood was observed at 0.5 hours after the second dose (35.6 µg-equivalents/g; 161 nmol equivalents/g) and declined steadily to the final 6-hour sample (1.15 µg-equivalents/g; 5.20 nmol equivalents/g). Similarly, the maximum concentration of [^{14}C]-dicamba in plasma was observed at 0.5 hours after the second dose (53.4 µg-equivalents/g; 242 nmol equivalents/g) and declined steadily to the final 6-hour sample (1.81 µg-equivalents/g; 8.19 nmol equivalents/g). Plasma concentrations were consistently greater than those in whole blood.

TABLE 3. Mean (± SD) concentrations of total radioactive residues in whole blood and plasma after two oral doses of [^{14}C]-dicamba at 75 mg/kg/day to male rats. [a]

Time post-dose (hours)	Concentration			
	µg-equivalents/g		nmol equivalents/g	
	Whole blood	Plasma	Whole blood	Plasma
0.5	35.6 ± 5.1	53.4 ± 7.8	161 ± 23	242 ± 35
1	28.6 ± 6.7	43.3 ± 10.2	129 ± 30	196 ± 46
2	15.2 ± 6.2	23.1 ± 9.7	68.8 ± 28.1	105 ± 44
4	4.24 ± 1.01	6.45 ± 1.54	19.2 ± 4.6	29.2 ± 7.0
6	1.15 ± 0.96	1.81 ± 1.38	5.20 ± 4.34	8.19 ± 6.24

a Data were obtained from Tables 1 and 2 on pages 26-27 of MRID 51129104; n = 4 samples/time point.

2. **Duodenum kinetics:** Total amounts and concentrations of radioactivity in the duodenum sections and mincing solutions and scrapings are presented in Table 4.

a. **Duodenum sections:** In the duodenum sections, mean total radioactivity and mean concentrations of radioactivity were greatest at 0.5 hours after the second dose and declined with time. Mean total radioactivity in section A declined from 6.07 µg-equivalents to 0.185 µg-equivalents, section B declined from 2.39 µg-equivalents to 0.158 µg-equivalents, and section C declined from 2.31 µg-equivalents to 0.118 µg-equivalents. Mean concentrations of radioactivity in the sections also were greatest at 0.5 hours after the second dose with concentrations that ranged from 20.9 µg-equivalents/g to 11.6 µg-equivalents/g (94.6 nmol equivalents/g to 52.5 nmol equivalents/g) in sections A, B, and C and declined with time. Concentrations were still measurable at 6 hours after the second dose with concentrations ranging from 0.536 µg-equivalents/g to 0.504 µg-equivalents/g (2.28 nmol equivalents/g to 2.43 nmol equivalents/g). Concentrations in duodenum sections were greatest in section A (immediately after the stomach) and declined from sections A to B and generally declined from sections B to C between 0.5-2 hours after the second dose. At 0.5 hours, mean concentrations in section A were 20.9 µg-equivalents/g (94.6 nmol equivalents/g) declining to 6.62 µg-equivalents/g (30 nmol equivalents/g) at 2 hours. Mean concentrations in section B at 0.5 hours were 13.3 µg-equivalents/g (60.2 nmol equivalents/g) declining to 5.33 µg-equivalents/g (24.1 nmol equivalents/g) at 2 hours. Mean concentrations in section C at 0.5 hours were 11.6 µg-equivalents/g (52.5 nmol equivalents/g) declining to 5.92 µg-equivalents/g (26.8 nmol equivalents/g) at 2 hours. At 4 and 6 hours, mean concentrations were generally similar across all sections.

b. **Mincing solutions and scrapings:** Mean total amounts of radioactivity in section A ranged from 0.045 µg-equivalents to 0.001 µg-equivalents, section B ranged from 0.016 µg-equivalents to 0.001 µg-equivalents, and in section C ranged from 0.013 µg-equivalents to <0.001 µg-equivalents. Mean concentrations of radioactivity were greatest at 0.5 hours, ranging from 0.025 µg-equivalents/g to 0.007 µg-equivalents/g (0.114 nmol equivalents/g to 0.032 nmol equivalents/g) and declined with time, approaching the limit of quantification at 6 hours.

TABLE 4. Mean (± SD) concentrations of total radioactive residues in duodenum sections and mincing solution and scrapings after two oral doses of [^{14}C]-dicamba at 75 mg/kg/day to male rats. [a]

Time post-dose (hours)	Concentration					
	Duodenum sections			Mincing solution and scrapings		
	Total radioactivity (µg-equiv.)	Concentrations (µg-equiv./g)	Concentrations (nmol equiv./g)	Total radioactivity (µg-equiv.)	Concentrations (µg-equiv./g)	Concentrations (nmol equiv./g)
0.5						
Section A	6.07 ± 2.81	20.9 ± 8.4	94.6 ± 38.0	0.045 ± 0.036	0.025 ± 0.019	0.114 ± 0.085
Section B	2.39 ± 0.71	13.3 ± 4.4	60.2 ± 20.1	0.016 ± 0.006	0.009 ± 0.003	0.038 ± 0.015
Section C	2.31 ± 0.93	11.6 ± 2.0	52.5 ± 9.0	0.013 ± 0.004	0.007 ± 0.003	0.032 ± 0.013
1						
Section A	4.39 ± 1.98	14.5 ± 7.6	65.6 ± 34.2	0.020 ± 0.009	0.011 ± 0.005	0.049 ± 0.022
Section B	1.96 ± 0.63	9.69 ± 2.53	43.8 ± 11.4	0.009 ± 0.003	0.005 ± 0.002	0.024 ± 0.009
Section C	2.03 ± 0.65	8.71 ± 1.75	39.4 ± 7.9	0.007 ± 0.003	0.005 ± 0.001	0.022 ± 0.004
2						
Section A	2.22 ± 1.14	6.62 ± 2.71	30.0 ± 12.3	0.007 ± 0.002	0.004 ± 0.001	0.017 ± 0.004
Section B	1.25 ± 0.60	5.33 ± 2.03	24.1 ± 9.2	0.004 ± 0.002	0.003 ± 0.001	0.013 ± 0.004
Section C	1.31 ± 0.59	5.92 ± 2.16	26.8 ± 9.8	0.004 ± 0.002	0.003 ± 0.001	0.012 ± 0.006
4						
Section A	0.574 ± 0.180	1.82 ± 0.38	8.24 ± 1.72	0.002 ± 0.001	0.001 ± 0.001	0.006 ± 0.002
Section B	0.357 ± 0.152	1.53 ± 0.50	6.92 ± 2.28	0.002 ± 0.001	0.001 ± 0.001	0.006 ± 0.002
Section C	0.363 ± 0.112	1.81 ± 0.87	8.19 ± 3.95	0.003 ± 0.002	0.002 ± 0.001	0.007 ± 0.005
6						
Section A	0.185 ± 0.095	0.504 ± 0.290	2.28 ± 1.31	0.001 ± <0.001	0.001 ± <0.001	0.005
Section B	0.158 ± 0.154	0.534 ± 0.396	2.42 ± 1.79	0.001 ± <0.001	0.001 ± <0.001	0.005
Section C	0.118 ± 0.099	0.536 ± 0.440	2.43 ± 1.99	<0.001 ± <0.001	<0.001	<0.001

a Data were obtained from Tables 3-8 on pages 28-33 of MRID 51129104; n = 4 samples/time point.

3. **Liver kinetics:** Liver kinetics are presented in Table 5. The mean concentration of radioactivity was greatest at 0.5 hours after the second dose (17.4 µg-equivalents/g; 78.7 nmol equivalents/g) and declined with time to 6 hours (0.98 µg-equivalents/g; 4.45 nmol equivalents/g).

TABLE 5. Mean (± SD) concentrations of total radioactive residues in liver samples after two oral doses of [^{14}C]-dicamba at 75 mg/kg/day to male rats. [a]

Time post-dose (hours)	µg-equivalents/g	nmol equivalents/g
0.5	17.4 ± 2.7	78.7 ± 12.3
1	13.7 ± 3.3	62.0 ± 14.8
2	7.75 ± 2.49	35.1 ± 11.3
4	2.88 ± 0.86	13.0 ± 3.9
6	0.983 ± 0.554	4.45 ± 2.51

a Data were obtained from Tables 10 and 11 on pages 35-36 of MRID 51129104; n = 4 samples/time point.

4. **Urine:** Urine data are presented in Table 6. Radioactivity was detectable in the urine at 1 hour following the first dose (1020 µg-equivalents/g), with the greatest concentration at 4 hours (4680 µg-equivalents/g). Radioactivity concentrations fell with time to a low of 111 µg-equivalents/g at 24 hours after the first dose. Following the second dose, radioactivity concentrations began to rise, with the greatest concentration at 2 hours after the second dose (6040 µg-equivalents/g) falling with time to the final collection at 6 hours (5570 µg-equivalents/g).

TABLE 6. Mean (± SD) concentrations of total radioactive residues in urine samples after two oral doses of [^{14}C]-dicamba at 75 mg/kg/day to male rats. [a]

Sample (day + hours)	µg-equivalents/g
Day 1, 1 hour	1020 ± 1170
Day 1, 2 hours	4060 ± 4710
Day 1, 4 hours	4680 ± 2300
Day 1, 6 hours	2580 ± 1010
Day 1 24 hours	111 ± 32
Day 2, 1 hour	597 ± 62
Day 2, 2 hours	6040 ± 4240
Day 2, 4 hours	4460 ± 3040
Day 2, 6 hours	5570 ± 8550

a Data were obtained from Table 9 on page 34 of MRID 51129104; n = 4 samples/time point.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: Dicamba is rapidly absorbed following oral administration to male rats, with maximum mean radioactivity concentrations observed in whole blood, plasma, liver, and duodenum occurring at 0.5 hours post dose (first sampling time).

Mean concentrations of [^{14}C]-dicamba between duodenum sections A, B and C showed that section A (the first 0-2 cm after the stomach) contained the greatest concentrations at earlier time points (0.5-2 hours). At later time points (4 and 6 hours), mean concentrations between duodenum sections were generally similar, indicating a more uniform distribution of radioactivity within the duodenum.

B. REVIEWER COMMENTS: No clinical signs of toxicity were reported.

The maximum concentration of [^{14}C]-dicamba in whole blood was observed at 0.5 hours after the second dose and declined steadily to the final 6-hour sample. Similarly, the maximum concentration of [^{14}C]-dicamba in plasma was observed at 0.5 hours after the second dose and declined steadily to the final 6-hour sample. Plasma concentrations were consistently greater than those in whole blood.

In the duodenum sections, mean total radioactivity and mean concentration of radioactivity were greatest at 0.5 hours after the second dose and declined with time. Concentrations were still measurable at 6 hours after the second dose. Concentrations in duodenum sections were greatest in section A (immediately after the stomach) and declined from sections A to B and generally declined from sections B to C between 0.5-2 hours after the second dose. At 4 and 6 hours, mean concentrations were generally similar across all sections. Mean total radioactivity and mean concentrations of radioactivity in the mincing solutions and scrapings were less than those found in the duodenum sections and followed the same time course, approaching the limit of quantitation at 6 hours. Mean concentrations of radioactivity in the liver sections were greatest at 0.5 hours after the second dose and declined with time to 6 hours.

Radioactivity was detectable in the urine at 1 hour following the first dose with the greatest concentration at 4 hours. Radioactivity fell to the lowest concentration at 24 hours after the first dose. Following the second dose, radioactivity concentrations began to rise, with the greatest concentration at 2 hours after the second dose and falling with time to the final collection at 6 hours.

The Reviewers agree with the Investigators' conclusions.

This study is classified as **acceptable / non-guideline**.

C. **STUDY DEFICIENCIES:** The following deficiency was noted:

- Formulation analyses were not reported.